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STUDY OF THE KINETICS OF THE RELEASE OF NIMESULIDE FROM A POLYMER SOLID DISPERSION SYSTEM

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Nowadays, non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most used symptomatic drugs in the modern world, as they can simultaneously exhibit anti-inflammatory, antipyretic, analgesic and antirheumatic effects [1]. Among the wide variety of NSAIDs, nimesulide-based drugs are among the most frequently used in practice for the treatment of various conditions of pain, fever, and inflammation. This active pharmaceutical ingredient (API) is able to affect a large number of mediators involved in inflammatory processes. Nimesulide, like most nonsteroidal anti-inflammatory APIs, belongs to class II according to the biopharmaceutical classification, that is, it is characterized by high permeability, but has low solubility in water (~0.01 g/l) [2]. In this regard, nimesulide is slowly released from solid oral dosage forms, and accordingly, the rate of its absorption from the gastrointestinal tract into the blood is also slowed down. This creates prerequisites for the use in medical practice of excessive doses of nimesulide and the occurrence of undesirable side effects. Therefore, increasing the solubility of nimesulide while maintaining high permeability to biological membranes is an actual issue.

In recent years, the formation of solid dispersion systems (SDS), which represent the dispersion of one or more active ingredients in an inert carrier in a solid state, is considered to be the most useful pharmaceutical technology for increasing the solubility, absorption, and therapeutic efficacy of hydrophobic APIs. Particles in solid dispersions have a reduced size, mostly amorphous state, as well as a higher degree of porosity and wettability, which allows to significantly increase the solubility of sparingly soluble APIs [3].

That is why, to increase the solubility of nimesulide, the technology of solid dispersion systems was applied. SDS of nimesulide was formed by solvent evaporation using polyvinylpyrrolidone K-25 (PVP K-25) as a polymer carrier. The study of dissolution profiles was carried out on a VK7000 vane dissolution device with a VK750D water heater (Vankel, USA) according to the method EPh 8.0 (2.9.3). The volume of the dissolution medium was 900 ml, the speed of rotation of the blade was 50 rpm, and the temperature was 37 °C. When studying dissolution profiles of nimesulide, it was taken into account that API is a weak acid with low solubility in water, so the use of standard media with low pH values (1.2 and 4.5) for comparison of dissolution profiles is unacceptable. Therefore, the research was carried out in buffer environments with a pH of 6.8; 7.5 and 7.8 (phosphate buffer solutions). The concentration of nimesulide was determined by the spectrophotometric method in the ultraviolet region on an OPTIZEN POP UV/VIS spectrophotometer (Mecasys, South Korea) at a wavelength of 400 nm. "Aulin", granules for oral suspension, 100 mg/2 g, was used as a comparison drug (Angelini Pharma, Czech Republic).

According to the results of the "Dissolution" test, it was established that the formation of SDS by solvent evaporation had a significant effect on improving the solubility of nimesulide. When studying the kinetics of the release of nimesulide in a buffer medium of pH=6.8, a more intense release of nimesulide from SDS was observed in the first minutes compared to the original drug. The degree of release of nimesulide from SDS in the first 5 min. was about 14%, while the comparison drug showed only 8% API release. For 10 min. during the test, the degree of release of nimesulide from SDS increased to 16%, while the indicators of "Aulin" remained at the same level. At the end of the experiment, the degree of dissolution of nimesulide was 18%, and "Aulin" was only 11% ($p<0.05$). In the buffer environment pH=7.5, the degree of release of nimesulide from the polymer SDS in the first 5 minutes was 55%, which is 1.3 times more compared to the original drug "Aulin". After 90 min. from the beginning of the study, the degree of nimesulide released from the SDS composition was more than 77%, while "Aulin" showed only 59% ($p<0.05$). The degree of release of nimesulide from SDS in buffer medium pH=7.8 is also higher than that of "Aulin". At the beginning of the experiment (5 min.), the degree of release of nimesulide from SDS was 1.44 times higher compared to the original drug. At the end of the study, the degree of nimesulide released from the SDS composition was more than 90%, while "Aulin" showed 80% ($p<0.05$).

It was concluded that the introduction of nimesulide into a solid dispersion system based on a water-soluble polymer carrier by the method of solvent evaporation improves the degree of release of nimesulide in all studied buffer media in comparison with the original drug, and the obtained SDS can be used as an API for the preparation of a highly soluble anti-inflammatory drug.

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